## II. REMARKS

Claims 35 to 60 are pending in the subject application. Claims 35 to 46 have been canceled without prejudice or disclaimer. Applicants respectfully reserve the right to file one or more claims directed to the canceled subject matter in a continuation and/or divisional application. Claims 47 to 60 were examined. By this Preliminary Amendment, claims 47, 48 and 55 to 59 were amended. Support for the amendments are found throughout the specification as filed. Thus, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Amended claims 47 to 60 are presently under examination.

In view of the preceding amendments and the following remarks, reconsideration and withdrawal of the rejections are respectfully requested.

### Objection to the Specification

The disclosure was objected to because the word "thymidylate" was misspelled in the claims and throughout the specification. The word has been corrected in the claims. Applicants respectfully defer amendment of the specification until allowable subject matter has been indicated by the Office.

### 35 U.S.C. § 112, Second Paragraph

Claims 47-60 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regard as the invention. The claims stand rejected on three grounds:

(a) The term "suitability" in claims 46-56 is alleged to be a relative term which renders the claim indefinite.

(b) Regarding claim 59, the phrase "or the like" is alleged to render the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "or the like'), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

(c) Claims 57-60 are alleged to be written in such general terms which are not particular to "screening for the effectiveness of TS directed drug therapy" that the "instructions



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for use of the kit" are *non sequitur*. The Office argued that it is unclear what method(s) is contemplated to be performed such that one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicants respectfully traverse. Without conceding the correctness of the Office's position, the claims have been amended in a sincere effort to overcome the grounds for rejection. In view of these amendments, reconsideration and withdrawal of these rejections are respectfully requested.

**35 U.S.C. § 102(b)**

Claims 47-49 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Leichmann et al. (1997) (J. Clin. Oncol. 15(10):3223-3229) taken with Horie et al. (1995) (Cell Struct. Funct. 20:191-197). The Office alleged that Leichmann et al. disclose the claimed method for determining the suitability of treating a cancer in a subject with a chemotherapeutic drug comprising taking a biological sample (colorectal cancer biopsy) of a subject and using the sample to determine the intratumoral expression of the TS gene which determined the response of the subject (page 3226, last paragraph). The Office opined that recitation in claim 47, "to determine the genotype of a gene of a subject" is inherent in the reference method because it was known in the art that the genotype of the TS gene determined the expression as taught, for example, by Horie et al. (abstract, last three lines).

Applicants respectfully traverse. The amended claims are directed to a method for screening cancer cells for sensitivity to a chemotherapeutic drug by taking a biological sample of said cancer cells from a subject; and determining the genotype of a pre-selected gene of the cancer cells, wherein said genotype determines the intratumoral expression of said gene, and correlating said gene expression to said sensitivity to said chemotherapeutic drug.

Leichmann et al. does not disclose determining the genotype of a pre-selected gene. Leichmann et al. discloses determining the expression level of the TS gene by determining the mRNA expression level of the TS gene, not the genotype. However, the Office alleged that the Horie et al. references connects the TS genotype to overexpression of the TS gene product. Applicants respectfully traverse. The cells assayed in the Horie et al. reference were transiently transfected with a cloned TS gene, which the Office assumed would have the same "genotype"

and phenotype as a cell isolated from a subject. However, the Office overlooked the authors teaching that regulation of the TS gene and thus regulation of its expression level not only occurs at the transcription level but also at the translation level (see page 191, left column, first full paragraph). Thus, contrary to the Office's assertion, it is not inherent that overexpression measured in the cells described in the Leichmann et al. reference is the result of the genomic polymorphism described in the artificial cell system (transiently transfected cells of Horie et al.). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). Accordingly, the Leichmann et al. reference does not anticipate the claims. Reconsideration and removal of the rejection under 35 U.S.C. § 102 is respectfully requested.

**35 U.S.C. § 103(a)**

Claims 47-56 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Leichmann et al. (1997) (J. Clin. Oncol. 15(10):3223-3229) in view of Horie et al. (1995) (Cell Struct. Funct. 20:191-197). The Office argued that the recitation in claim 47, "to determine the genotype of a gene of a subject" is inherent in the reference method because it was known in the art that the genotype of the TS gene determined the expression as taught, for example, by Horie et al. (abstract, last three lines).

Regarding claim 50, the Office argued that Horie et al. determined the genotype of the TS gene wherein the TS gene has a 28 bp tandem repeat in the 5' UR. (page 194, Figure 4) which is polymorphic in the number of repeats, two or three, in human subjects (abstract). The Office opined that therefore, it would have been known to one of ordinary skill in the art at the time the claimed invention was made that TS genotypes included homozygous for a triple repeat, heterozygous for a triple and a double repeat and homozygous for a double repeat based on general knowledge in the art of the presence of two copies or alleles of each gene in human subjects.

Regarding claims 51-54, the Office alleged that Leichmann et al. disclose the chemotherapeutic TS directed drug, 5-fluorouracil, a fluoropyrimidine, and human subjects

(abstract). The Office remarked that regarding claims 55 and 56, Leichmann et al. extracted TS mRNA for direct determination of TS expression by RT-PCR (page 3224 at "Laboratory Methods"). The Office stated that however, one of ordinary skill in the art would have been motivated to determine genotype by analyzing genomic DNA instead of mRNA as in the references for the known benefit of reducing the time, labor and cost of the analyses. Analysis of PCR products by electrophoresis was routinely practiced in the art.

Claims 57-60 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Leichmann et al. in view of Horie et al. as applied to claims 447-56 above and further in view of routine practice in the art. The Office opined that the claimed invention differs from the teachings of Leichmann et al. and Horie et al. wherein means for determining a genomic polymorphism of the TS gene, for use in screening for the effectiveness of TS directed drug therapy in human subjects are provided in a kit including instructions for use and wherein all or some of the positive and negative controls, primers, sequencing markers and probes for determining the presence of a tandemly repeated 28 base-pair nucleic acid sequence that defines the genomic polymorphism in the 5' UTR of the TS gene in solution or as a dispersion are included. The Office stated that however, the skilled practitioner in the art would have been motivated to provide the reagents, controls and polymorphic DNA of Horie et al., especially the DNA tandemly repeated sequences, in a kit in view of routine practice in the art and of the teachings of Leichmann et al. of the relationship between the TS polymorphism and the effectiveness of chemotherapy for the known benefits of ease of use and commercial applications.

Applicants respectfully traverse. Applicants respectfully submit that the references fail to teach or suggest the invention of claims for the reasons provided above. Leichmann does not disclose that an altered phenotype is predictive of gene expression (TS). Horie et al. discloses that in cells transiently transfected with a cloned TS gene, these cells do overexpress TS. However, the Office failed to consider the "teaching away" present in Horie et al., i.e., that TS overexpression can be regulated at the translational as well as the transcriptional level. The assay of Leichmann et al. would not detect translational regulation of TS protein production. Thus, the combination of the references fail to teach or suggest the invention of the claims. For this reason, the rejection is improper and therefore should be withdrawn.

## III. CONCLUSION

No additional fee is deemed necessary in connection with the filing of this Preliminary Amendment and Response. However, if the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-2518**, referencing billing no. 7000722001. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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